## REMARKS

### I. Status of the Claims

Applicant acknowledges with appreciation that the Office has withdrawn the previous rejections under 35 U.S.C. § 103(a). Office Action, page 2. Claims 2 and 3 are under consideration.

### II. Rejections Under 35 U.S.C. § 103(a)

The Office newly rejects claim 2 under 35 U.S.C. § 103(a) as allegedly unpatentable over JP 2000-281584 to Yamanouchi Pharmaceuticals ("Yamanouchi") in view of Levine *et al.*, Int Conf AIDS (1989) 5:406 ("Levine") Nissen *et al.*, Blood (1998) 72:2045-72 ("Nissen") and Weisbart *et al.*, Nature (1985) 314:361-63 ("Weisbart"). Office Action, page 3.

In addition, the Office newly rejects claims 3 under 35 U.S.C. § 103(a) as allegedly unpatentable over JP 2000-281584 to Yamanouchi Pharmaceuticals ("Yamanouchi") in view of Kojima *et al.*, Blood (1991) 77:937-41 ("Kojima") and Falanga *et al.*, Blood (1999) 93:2506-14 ("Falanga"). . Office Action, page 4.

Applicant respectfully traverses each of these rejections at least because the combination of references does not provide a technical basis from which the ordinary artisan could have reasonably expected that the composition recited in the claims could be used to treat neutropenia, as recited in claim 2, or aplastic anemia, as recited in claim 3.

"The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." M.P.E.P. § 2142. The Office must make several basic factual inquiries to determine whether the claims of a patent application are obvious

under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere*, require the Examiner to: (1) Determine the scope and content of the prior art; (2) Ascertain the differences between the prior art and the claims in issue; (3) Resolve the level of ordinary skill in the pertinent art; and (4) Evaluate evidence of secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). The obviousness or non-obviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Id.*; *see also KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 405, 82 U.S.P.Q.2d at 1391 (2007). Specifically, once the findings of fact are articulated, the Office "must then make a determination whether the claimed invention 'as a whole' would have been obvious at the time to that person." *Id.*

A *prima facie* case of obviousness also requires that the references relied upon provide a reasonable expectation that their teachings could successfully be combined or modified in the manner proposed by the Office. M.P.E.P. § 2143.02. The requirement for a reasonable expectation of success is apparent in the Supreme Court's decision in *KSR Int'l* which notes that it is "predictable" variations that are unpatentable under 35 U.S.C. § 103(a). *KSR Int'l*, 550 U.S. at 417, 82 U.S.P.Q.2d at 1396. In accord with the Court's guidance, the rationales set forth in the M.P.E.P. § 2143 all share in common a requirement for "predictability" and "predictable results." Further, predictability must flow from the teachings of the references: it is improper to rely on Applicant's disclosure. *See, e.g., Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1515-16 (Fed. Cir. 2004).

In this case, the references relied upon by the Office fail to provide a reasonable expectation that the composition recited in the claims would have the property of

increasing GM-CSF production *in vivo*, as disclosed in the working examples to thereby provide therapeutic benefit in treating neutropenia or aplastic anemia. This is because the teachings of Yamanouchi, the primary reference in each rejection, are drawn to a biologically distinct function—neutrophil *activation*—than is required to provide a logical combination with the secondary references regarding treatment of neutropenia (claim 2) and aplastic anemia (claim 3).

Yamanouchi teaches that a neutrophil-activating agent is obtained when a crude drug is prepared using the plants *Cucurbita moshata*, *Carthamus tinctorius*, *Plantago asiatica*, and *Lonicera japonica*. Abstract. The neutrophil-activating activity is demonstrated by showing that the crude drug increased the sterilizing ability of neutrophils and their phagocytic activity. Yamanouchi at [0021-0022] of English translation. However, the migration ability of the neutrophils in the experimental group was the same as the controls. *Id.* at [0021]. Neutrophil activation is important in eliminating bacteria during infections. *Id.* at [0002].

The secondary references upon which the Office relies in the rejection of claim 2 show that 1) GM-CSF is a neutrophil activating factor (Weisbart) and that 2) GM-CSF can be used to treat neutropenia (Levine). Similarly, the secondary references relied upon in the rejection of claim 3 show that 1) G-CSF is a neutrophil activating factor (Falanga) and that 2) G-CSF can be used to increase the neutrophil count to treat aplastic anemia (Kojima). Based on these observations, the Office alleges that it would therefore have been obvious to use the neutrophil-activating crude drug of Yamanouchi in methods of treating neutropenia and aplastic anemia.

However, the rationale for using the crude drug of Yamanouchi presumes that the reason that GM-CSF treats neutropenia and G-CSF treats aplastic anemia is because those growth factors *activate* neutrophils. That assumption does not follow because, as discussed below, the references relied upon by the Office all teach that it is the ability of GM-CSF and G-CSF to promote proliferation and differentiation of neutrophil progenitors so that the number of circulating neutrophils increases that provides a rationale basis for using those factors in treating neutropenia and aplastic anemia. Neutrophil activation, the activity taught by Yamanouchi, is biologically distinct from this initial differentiation process.

It was well known in the art that neutrophils play an important role in inflammation and that their differentiation and activation proceeds along a multi-step process. For convenience, Applicant provides a copy of the review chapter "Inflammation" by Rosenberg & Gallin in the textbook FUNDAMENTAL IMMUNOLOGY, Fourth Edition, ed. W. Paul, Lippincott-Raven Publishers 1999 ("Rosenberg & Gallin"), that provides an overview of both the role of neutrophils in inflammation and other aspects of their biology. In particular, the text on pages 1056-1058 describes the steps that lead to the development of the ability of neutrophils to mediate an inflammatory response. The first step in this process is the development and release of neutrophils from the bone marrow. Although this is a necessary step before neutrophil activation can take place, development and release into the circulation does not by itself result in activation. Instead, neutrophils in the circulation are initially quiescent and must undergo the two-step process of priming and activation before acquiring inflammatory activities.

As summarized in Table 1 on page 1058, both GM-CSF and G-CSF contribute to the process of neutrophil maturation so that the cells can be released into the circulation. In Table 1 this activity is described as "stimulates maturation within the bone marrow." In addition, both GM-CSF and G-CSF also have roles in neutrophil priming. Thus, GM-CSF and G-CSF were known to act at two *distinct* steps in the multi-step process that leads to the development of effector function in neutrophils.

It is the neutrophil-activating property of GM-CSF that Weisbart describes. Not only does the abstract the Office provides refer explicitly to activation, the superoxide anion generation in response to f-MLP it references is a test of priming and activation, as noted on page 1057 of Rosenberg & Gallin. In contrast, the study of Levine looks at the effect of GM-CSF on increase in neutrophil *counts*; that is, release of neutrophils from the bone marrow. It is the increase in neutrophil numbers that is relevant for treatment of neutropenia, which is literally a state of low neutrophil numbers. It is likewise the increase in neutrophil numbers following GM-CSF treatment that Nissen considers important. Nissen, p. 2047 ("Since severe neutropenia is a poor prognostic factor in aplastic anemia patients . . . attempts to increase circulating neutrophil counts with hematopoietic lymphokines seems warranted . . . ."). Thus, the therapeutic basis for treatment of neutropenia is the ability of a drug to increase neutrophil counts, not to activate a neutrophil.

Similarly, while Falanga teaches that G-CSF can activate neutrophils, it is the ability of G-CSF to stimulate the "proliferation and differentiation of hematopoietic progenitor cells (HPCs) from bone marrow . . . [that] justif[ies] the expanding use of recombinant G-CSF (rHuG-CSF) in clinical conditions, including chronic idiopathic

neutropenia . . . ." Falanga, p. 2056. Kojima likewise looks to the increase in neutrophil count as the rationale for using G-CSF in treating aplastic anemia. Kojima, Abstract.

Increasing the neutrophil count does indirectly improve the ability of a neutropenic or aplastic anemic patient to combat infection because there are more neutrophils available for activation. But while GM-CSF and G-CSF contribute both to increase in neutrophil numbers and to neutrophil priming/activation, it was well known that not all drugs have both effects. For example, of the 10 agents listed in Table 1 of Rosenberg & Gallin, only GM-CSF and G-CSF act on neutrophils to promote their maturation within the bone marrow. The other factors act on one or more aspects of the priming and activation process.

As noted, Yamanouchi's teachings are only with respect to the effect of the crude drug derived from *Cucurbita moshata*, *Carthamus tinctorius*, *Plantago asiatica*, and *Lonicera japonica* on the sterilizing ability and phagocytic activity of the neutrophil. In contrast, it is Applicant's disclosure that shows that a composition comprising certain weight percents of *Cucurbita moshata*, *Carthamus tinctorius*, *Plantago asiatica*, and *Lonicera japonica* has the ability to increase GM-CSF production *in vivo*. Nothing in the teachings of Yamanouchi provide a reasonable basis to predict that the crude drug would be able to increase GM-CSF activity. Further, since the references indicating that GM-CSF can treat neutropenia and aplastic anemia all indicate that the relevant function is increasing neutrophil counts, not increasing neutrophil activation, Yamanouchi also does not provide a reasonable basis to predict that the claimed composition could be used to treat neutropenia or aplastic anemia.

Applicant has discovered that the composition recited in the claims has a GM-CSF increasing activity. In fact, as described in Examples 1 and 4, the application of the present crude drug can increase GM-CSF even when applied to a person who is not suffering from inflammation. Indeed, the present crude drug does not contain GM-CSF itself since all of the effective ingredients of the crude drug are of plant origin. It is only once the ordinary artisan understands that the composition can increase levels of GM-CSF that there becomes a reasonable expectation that the composition could be used to treat conditions in which differentiation of neutrophils is impaired.

Applicant respectfully submits that the references cited by the Office do not provide a reasonable expectation of success in arriving at the claimed methods. For at least that reason, the Office has failed to carry its burden in establishing a *prima facie* case of obviousness. Applicant therefore respectfully requests that the Office withdraw the rejection.

## CONCLUSION

In view of the foregoing remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: _____
Jessica H. Roark
Reg. No. 54,869